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Mechanisms of the contextual interference effect in individuals post-stroke

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Abstract

Although intermixing different motor learning tasks via random schedules enhances long-term retention compared to "blocked" schedules, the mechanism underlying this contextual interference effect has been unclear. Furthermore, previous studies have reported inconclusive results in individuals post-stroke.

We instructed participants to learn to produce three grip force patterns in either random or blocked schedules, and measured the contextual interference effect by long-term forgetting: the change in performance between immediate and 24-hour post-tests. Non-disabled participants exhibited the contextual interference effect: no forgetting in the random condition, but forgetting in the blocked condition. Participants at least 3 months post-stroke exhibited no forgetting in the random condition, but marginal forgetting in the blocked condition. However, in participants post-stroke, the integrity of visuo-spatial working memory modulated long-term retention after blocked schedule training: participants with poor visuo-spatial working memory exhibited little forgetting at 24 hours.

These counter-intuitive results were predicted by a computational model of motor memory that contains a common fast process and multiple slow processes, which are competitively updated by motor errors. In blocked schedules, the fast process quickly improved performance, therefore reducing error-driven update of the slow processes, and thus poor long-term retention. In random schedules, interferences in the fast process led to slower change in performance, therefore increasing error-driven update of slow processes and thus good long-term retention. Increased forgetting rates in the fast process, as would be expected in individuals with visuo-spatial working memory deficits, led to small updates of the fast process during blocked schedules, and thus better long-term retention.

Introduction

During neuro-rehabilitation after brain injury, but also in activities such as sports, technical training, and music, one must often learn, or re-learn, multiple motor tasks within a given period. Intermixing the learning of different tasks via random schedules reduces performance during training, but enhances long-term retention compared to blocked schedules, e.g. (Schmidt and Lee 1999; Shea and Morgan 1979a; Tsuitsui et al. 1998). This phenomenon is known as the contextual interference (CI) effect.

Despite close to a century of research (Pyle 1919), the mechanism underlying the CI effect are unclear, however. According to the "forgetting-reconstruction" hypothesis of the CI effect, short-term forgetting between successive presentations of the same task during random training requires the learner to "reconstruct the action plan at each presentation", resulting in stronger memory representations (Lee and Magill 1983; Lee et al. 1985). Recent computational models similarly suggest a crucial role of working memory in the CI effect. It has notably been proposed that motor adaptation occurs via simultaneous update of a fast process that contributes to fast initial learning but forgets quickly, and a slow process that contributes to long-term retention but learns slowly (Joiner and Smith 2008; Smith et al. 2006). We recently extended this model to account for multiple task adaptation (Lee and Schweighofer 2009). In our model, a single fast process is arranged in parallel with multiple independent slow processes switched via contextual cues. During adaptation, motor errors simultaneously update fast and slow processes in a competitive manner. In a situation where tasks are intermixed during training, our model predicts that the decay in the fast process due to both time and interference from other tasks leads to greater update of the slow process. Thus, random schedule training should lead to less long-term forgetting than blocked schedule training, as in the CI effect.

Individuals with unilateral stroke-related damage in the sensori-motor areas often exhibit deficits in visuo-spatial working memory (Winstein 1999). Accordingly, the integrity of visuo-spatial working memory may play a role in the CI effect in individuals post-stroke. The two previous attempts at testing the CI effect in stroke individuals with motor impairments were inconclusive. Specifically, Hanlon (Hanlon 1996) reported a CI effect; the effect of schedules could not be unequivocally determined in this study, however, because the practice sessions were of variable lengths. On the contrary, Cauraugh and Kim (Cauraugh and Kim 2003) reported no CI effect; the tasks used in this study were strengthening tasks (such as wrist/finger extension), however, not goal-directed tasks that required acquisition of new skills. Thus, it is unclear whether these contrasted results are due to either, or both, the experimental design or the heterogeneous grouping of all stroke individuals post-stroke with potential differences in working memory, thus masking the CI effect.

The goals of this study are thus to provide a mechanistic explanation for the CI effect using our previous model (Lee and Schweighofer 2009), and notably study the role of the fast process in the CI effect, and to test the CI effect in individuals post-stroke with visuo-spatial working memory deficits, providing behavioral support for the model. For this purpose, we designed an experiment in which young non-disabled –participants and individuals at least 3 months post-stroke learned how to produce three specific force patterns in either a random or a blocked schedule practice condition. The CI effect was measured by long-term forgetting, the change in performance between two retention tests given immediately and 24 hour following training respectively.

Materials and Methods

Participants

Non-disabled -participants. Twenty-four young participants (12 females) with no reported neurological deficits were randomly assigned either to a blocked training schedule or to a pseudo-random training schedule (N = 12 in each group; because of problems with the recording device on day with 1 participant, we analyzed data for 11 participants in the random group and 12 in the blocked group for the retention results). The participants met the following inclusion criterion: be over 18 years of age and be right hand-dominant. Summary of the demographic data is reported in Table 1.

Individuals post-stroke. Twenty-five participants (7 females) with stroke at least three months from onset were randomly assigned either to a blocked training schedule or to a pseudo-random training schedule (N = 12 in blocked group, N = 13 in random group). To be included in the study, the participants needed to fulfill the following inclusion criteria: 1) greater than 18 years of age; 2) at least 3 months post stroke; 3) stable medical condition; 4) have a upper extremity Fugl-Meyer score no less than 33 (Fugl-Meyer et al., 1975); 5) ability to produce at least 10 Newtons of force in power and 2 Newtons in precision grasp; 6) have a score at least 10 out of 17 on the Functional test of the Hemiparetic Upper Extremity (FTHUE) (Wilson, 1984); 7) have a score of no less than 25 on the mini mental state exam (MMSE). The participants were excluded from the study if they 1) demonstrated excessive pain in any joint of the more affected extremity that could limit ability to participate in the grasping tasks; 2) had any previous history of surgery of fracture in the affected extremity that may impair the ability to perform the task. Summary of the demographic data is reported in Table 2.

All participants (non-disabled individuals and individuals post-stroke) signed an informed consent to participate in this study, which was approved by the IRB at the University of Southern California.

Experimental design and procedures

A critical impairment after stroke is the inability to generate precise force output at moderate levels with sufficiently rapid force rise. We thus designed a learning experiment that required learning to exert three force patterns with unique magnitude and timing in response to three visually distinct target force profiles. Participants were pseudo-randomly assigned to either a blocked schedule condition or a random schedule condition.

The participants came to our laboratory for two sessions on two consecutive days. The first session consisted of physical and cognitive tests, a training session, and an immediate retention test (see below). A delayed retention tests was given 24 hours following the first (immediate) retention test. During the training session, all participants were trained on the three motor tasks, with 50 trials per task. In the blocked schedule condition, there were three blocks of 50 consecutive trials, with a single task within a block. Task order was counterbalanced across participants. In the random schedule condition, there were 50 blocks of three trials, with each task occurring once per block at a random order within the block. The initial task order was counterbalanced across participants.

The participants were instructed to reach and grasp a plastic cylinder, and exert a force profile with a power grasp that matched one of three target profiles displayed on a computer screen in both magnitude and timing (Figure 1). Participant post-stroke were instructed to use their affected hand. Non-

disabled participants were instructed to use their dominant hand. Force data was acquired through a sensor embedded in the cylinder sampling at a rate of 100 Hz.

At the beginning of each trial, one of the three target force profiles was shown. Two seconds later, the target profile disappeared, a “GO” signal was displayed, and the participants were instructed to produce a force trajectory that matched the target force profile. If the participant did not grasp the cylinder within the 2 seconds of the “GO” signal, the message “Next time move faster” was displayed.

In training trials, feedback was provided four seconds after the end of the target display. Specifically, the actual force trajectory was shown superimposed on the desired trajectory (Figure 1). An error value was also displayed indicating the total root mean squared error (RMSE) between the desired and actual force trajectory.

To assess performance after training, retention tests were given immediately and 24-hour following training. Each test consisted of five trials per task, with each trial similar to training trials, but without feedback. In the immediate test for the blocked schedule group, the test for each task was given immediately following the 50 training trials. In the immediate retention tests for the random schedule group, as well in the delayed tests for both groups, the order of the three tasks was randomized.

For each participant, maximal force was recorded with the apparatus in three separate trials and averaged prior to training. The maximum magnitude of each target force profile was set at 40% of maximum force for each participant.

Figure 2 shows examples of the force profiles and the actual force trajectories for one force pattern for a representative participant in each group (stroke blocked, stroke random, non-disabled

blocked, non-disabled random) for the first trial of training, for the first trial of the immediate test, and for the first trial of the delayed retention test.

Visuo-spatial working memory test

In our task, participants exerted grip forces based on line-drawing cues visually displayed 2 seconds ago and not available during force modulation. Furthermore, visual feedback was provided 4 seconds following force modulation. Thus, visuo-spatial working memory was needed to link the visual information provided as cue and feedback to the actual movement generated. We assessed visuo-spatial working memory for each participant with the figural memory subtest of the Wechsler Memory Test revised (WMS-R; (Wechsler 1987)). In the figural memory test, a target geometrical pattern is presented to the participant. After a 6 second delay, both the target pattern and alternative patterns are shown. The participant is asked to identify the correct pattern. The maximum score for the figural test is 10. The figural test has been used in previous research studies with various clinical populations to assess visual-visuo-spatial working memory, e.g. (Hawkins et al. 1997; Nixon et al. 1987; Winstein et al. 1999). The digital memory subtest of the Wechsler Memory Test was also given for comparison purpose.

Data analysis

To compare performance across two schedules and across young non-disabled and stroke individuals, we computed performance at each trial as 1 minus a normalized root mean square error (nRMSE) averaged across the tasks. We normalized the RMSE for each task, we divided the RMSE at each trial by the difference between the maximum RMSE (often, but not always on the first trial) and the minimum RMSE generated during training. The nRMSE for subject i at trial n is thus given by:

$$nRMSE_i(n) = \frac{RMSE_i(n) - \min(RMSE_i)}{\max(RMSE_i) - \min(RMSE_i)}$$

Where, min(.) and max(.) are calculated for subject i across training trials for all three tasks

Our main dependent measure was "long-term forgetting". Long-term forgetting was computed as the difference in task performance between the immediate and the 24-hour test. As measure of retention performance in the immediate and delayed retention tests, we used the average performance in the first trial for the three tasks. We did not use all 5 trials of each task in the retention test, because we noted that performance largely improved during the test even without feedback in the non-disabled participant group; e.g., in immediate group, average of 3 tasks, repeated ANOVA for the 5 test trials, $p < 0.001$ in blocked condition, $p = 0.04$ in the random condition.

All data (and residuals for regression models) used were tested for normality with the Shapiro-Wilks' test, and for equality of variance with the Levene's test. For group comparisons, when the data were normally distributed and when the sample size was greater or equal to 10 in each group, we used t-tests for independent measures, and paired t-tests for repeated measures. Otherwise, we used the Mann-Whitney Test for independent measures. In repeated ANOVA, non-spherical data were corrected using Greenhouse-Geisser correction. Difference between groups in participants baseline characteristics were tested with t-tests when the data were numerical (e.g. age) and with chi-square tests when the data were categorical (e.g., gender). We classified the individuals with stroke as "high" and "low" function in visuo-spatial working memory, based on a cut-off of 7 on the figural Wechsler score (the cut-off value was chosen because it yielded near equal group sizes in our data set) and compared the effect of practice schedules for high and low level groups. Our significance level in all tests was set at $p < 0.05$.

Computer modeling

It has been proposed that motor adaptation occurs via simultaneous update of a fast process that contributes to fast initial learning but forgets quickly, and a slow process that contributes to long-term retention but learns slowly (Joiner and Smith 2008; Smith et al. 2006). We recently extended this model to account for multiple task adaptation (Lee and Schweighofer 2009). In our model, a single fast process is arranged in parallel with multiple independent slow processes switched via contextual cues. During adaptation, motor errors simultaneously update the fast and the selected slow processes in a competitive manner. Because the model was specifically developed to account for multiple task-adaptation, it can be used to simulate the changes in performance resulting from different task schedules. We therefore tested in what conditions, if any, the model could reproduce the contextual interference effect.

The model contains one fast process, and N slow processes, N being the number of tasks, all organized in parallel (the model is thus called a 1-Fast N-Slow parallel model). The model output and the state update rules are given by equations (1) and (2), respectively:

$$y(n) = x_f(n) + \mathbf{x}_s(n)^T \mathbf{c}(n) \tag{1}$$

$$\begin{aligned} x_f(n+1) &= A_f x_f(n) + B_f e(n) \\ \mathbf{x}_s(n+1) &= A_s \mathbf{x}_s(n) + B_s e(n) \mathbf{c}(n) \end{aligned} \tag{2}$$

where n is the trial number, the motor error determined by the difference between an external perturbation $f(n)$ and the motor output $y(n)$ at time step n $e(n) = f(n) - y(n)$, x_f the state of the fast process, $\boldsymbol{x_s}$ the state vector of the slow process, and $\boldsymbol{c}$ the contextual cue vector;, with both $\boldsymbol{x_s}$ and $\boldsymbol{c}$ vectors have a length equal to the number of tasks N. Because, we assumed no interference and perfect switching among states in the slow process in the model, $\boldsymbol{c}$ is a unit vector with a single non zero element. A_f is the forgetting rate of the fast process, A_s the forgetting rate of the slow processes, B_f the learning rate of the fast process, and B_s the learning rate of the slow processes. Default parameters in the model in the current simulations were A_f=

0.8, B_f = 0.2; A_s = 0.995; B_s = 0.04 and were hand-tuned to qualitatively reproduce the learning curve of the non-disabled subjects in the blocked and random schedule.

At trial *n*, the motor output is generated by the sum of the fast process and the corresponding slow process, according to equation (1). After a task is presented, if the motor error is not zero, both the fast state and the corresponding slow state are updated according to equation (2). Because of the gating by the contextual input, the slow states for other (non-presented) tasks are not updated after this trial, but instead decay with forgetting rate A_s. When no tasks are presented, such as after training for instance, all fast and slow processes decay towards zero. Forgetting in the fast processes is rapid (in the order of tens of seconds), but forgetting in the slow processes more long-lasting (in the order of tens of minutes). Although we do not model long-term retention (in the order of days), it has been shown that for adaptation to one task, the amount of long-term retention is predicted the level of activity in the slow process at the end of training (Joiner and Smith 2008). Thus, to compare computer simulations to data in our experimental data, performance for the first task at the end of training was taken as immediate retention performance; level of the slow process for the first task at the end of training was taken as long-term retention at 24 hour.

In the present work, the competition between the fast and slow processes for errors is crucial to explain the differential effects of blocked and random schedules. Such competition stems from the model's parallel architecture. In our previous work (Lee and Schweighofer 2009), we showed that only the parallel 1-Fast N-Slow architecture, and not the serial 1-Fast N-Slow architecture, could account for adaptation data in a random schedule. Because of this parallel architecture of the model, the fast and slow processes compete for motor errors at each trial. Thus, in a blocked task presentation, there is no interference in the fast process, which is only updated by the errors of the task presented in the block. Because the fast process as a high learning rate (compare the values of the parameters B_f and B_s and above), errors will be quickly reduced. In a random schedule, however, there are large interferences in the

fast process; if the two perturbations have equal magnitude but opposite signs for instance, the fast process will have activity oscillating around zero. As a result, the changes in performance during training will be mostly driven by the slow process. We refer the reader to (Lee and Schweighofer 2009) for additional details of the model.

Additionally, we made the simplifying assumption that, in the model, the integrity of visuo-spatial working memory is linked to the rate of decay of the fast process, with larger rates of decay linked to poorer visuo-spatial working memory. We thus modeled the integrity of visuo-spatial working memory by modulating the time constant τ_f in the fast process, with $\tau_f = 1/(1- A_f)*T$, where A_f is the fast process forgetting rate given in equation (2) and T corresponds to a simulated trial length, which was 12 seconds as in the experiment. The default "normal" forgetting rate A_f =0.8 gives τ_f = 60 sec. Small time constant, which indicates fast decay in the fast process (small value of forgetting rate A_f), are used to model poor working memory. The "default" poor working memory forgetting rate was A_f= 0.4, which gives τ_f = 20 sec.

Results

The CI effect in the computational model

Our computational model reproduced the CI effect: slower improvements in performance during training (Figure 3 A and C blue lines) and less long-term forgetting following training in random schedules than in blocked schedules (Figure 3 B and D). During blocked presentations, the fast process exhibited high activity levels (Figure 3A green line) because there was little long-term forgetting during the short intervals between presentations of the same task. Because fast and slow processes compete for errors, the high activity levels of the fast process leads to relatively little update of the slow process

(Figure 3A red line). As a result, there was fast adaptation during training, but large long-term forgetting in delayed retention (Figure 3B). In contrast, during random presentations, the fast process exhibited low and jittered activity levels (Figure 3C green line); this occurred because interferences between tasks was high and passage of time between presentations of the same task was relatively long. This led to relatively large update of the slow process (Figure 3C red line). As a result, there was relatively slow adaptation during training, but little long-term forgetting in delayed retention (Figure 3D, compare to Figure 3B).Specifically, at the end of training and for task 1 for the blocked schedule, performance was 0.79, and the slow process was 0.57 (performance is equal to the slow process at long-term retention; see Methods); for the random schedule, performance was 0.73, and the slow process was 0.76.

Our model makes the prediction that the integrity of visuo-spatial working memory differentially affects delayed retention in blocked and random schedules. In Figure 4, a simulated participant with poor visuo-spatial working memory (parameter A_f= 0.4) showed little long-term forgetting following either blocked or random schedule training (Figure 4 B, D). During blocked schedule training (Figure 4A), compared to the simulated participant with normal visuo-spatial working memory of Figure3A, there was reduced update of the fast process because of large long-term forgetting from one trial to the next. However, because of the competition between fast and slow process, there was an enhanced update of the slow process (Figure 4A red line). Long-term forgetting following blocked training was then minimal (Figure 4B). During random schedule training (Figure 4C), the update of the slow process was nearly identical to that of the “normal” simulated participant (Figure 3C). Specifically, at the end of training and for task 1 for the blocked schedule, performance was 0.78, and the slow process was 0.71 (performance is equal to the slow process at long-term retention, see Methods); for the random schedule, performance was 0.72, and the slow process was 0.75.

In the model, long-term forgetting following blocked schedule training positively correlates with the time constant of visuo-spatial working memory: for small time constants (i.e., poor visuo-spatial

working memory), there was little long-term forgetting in the delayed test (Figure 5A left), because much short-term forgetting happened between presentations during training (as in Figure 4A). For larger time constants (i.e., good visuo-spatial working memory), there was large long-term forgetting in the delayed test (Figure 5A right), because little short-term forgetting happened between presentations during training (as in Figure 3A). In contrast, long-term forgetting following random schedule training did not correlate with this time constant (Figure 5B): because of interference between tasks during training, there was little build-up of fast process.

The CI effect in non-disabled individuals

We first examined whether the typical CI effect was replicated with our tasks in our young non-disabled sample. There was no difference in baseline characteristics between the two non-disabled groups for gender, age, power-grip maximal force, and Wechsler figural score in non-disabled participants (see Table 1).

Long-term forgetting was positive following blocked training (Blocked long-term forgetting: 0.183 ± 0.063; $p = 0.011$ one-sample t-test), but not following random training (long-term forgetting: -0.0004 ± 0.041; random: $p = 0.99$, one-sample t-test). Furthermore, long-term forgetting was greater following blocked schedule than following random training ($p = 0.023$, t-test) (see Figure 6C and D).

The performance of participants in both groups improved during training in both conditions (repeated measure ANOVA, 10 blocks of 5 trials, $p = < 0.0001$ for both blocked and for random groups) (Figure 6A and C). There was no difference in performance in the first block of 5 trials between groups ($p = 0.129$, t-test), no difference in the last block of 5 trials ($p = 0.233$, t-test), and no difference in the overall change in performance between the first and the last block of 5 trials ($p = 0.763$, t-test). However, performance continued to improve in the random group after the first 5 trials, but not in the blocked

group. To show this, we regressed the performance from trials 6 to 50 as a function of trial number for each participant: the slopes were positive in the random group (0.0051 ± 0.0006 $trial^{-1}$) but near zero in the blocked group (mean 0. 0015 ± 0.0011 $trial^{-1}$), and larger in the random group compared to the blocked group (p = 0.008, t-test).

The CI effect in individuals post-stroke

There was no difference in baseline characteristics between the two groups for gender, age, side of paresis, concordance of stroke (i.e. whether the stroke affected the dominant hand), time post-onset, maximal force, any of the Fugl-Meyer upper extremity subscale scores (range of motion, pain, sensory, arm motor, hand, wrist), FTHUE, MMSE, and Wechsler figural score (all values are given in Table 2). The only marginally non-zero difference between groups was power-grip maximal force (blocked: 462 ± 67 Newton; random: 326 ± 29 Newton, p = 0.082; t-test).

We first examined the CI effect for all individuals post-stroke (i.e. without dividing the participants into subgroups based on their figural memory test score). Long-term forgetting was marginally positive following blocked training, but not following random training (blocked 0.076 ± 0.040, p = 0.085, random: 0.0085 ± 0.063, p = 0.89, one sample t-tests) (see Figure 7C and D). Furthermore, long-term forgetting was not different following blocked and random training (p = 0.342, t-test) (see Figure 6C and D). We verified that there was no correlation between maximal power grip force and long-term forgetting in either group (blocked: p = 0.97; random: p = 0.75; Pearson).

The performance of participants in both groups improved during training in both conditions (repeated measure ANOVA, 10 blocks of 5 trials, p < 0.0001 for both groups; Greenhouse-Geisser corrections) (Figure 7A and C). There was no difference in performance in the first trial between groups

(p = 0.12, t-test). Furthermore, there was no difference in performance in the first block of 5 trials between groups (p = 0.13, t-test), no difference in the last block of 5 trials (p = 0. 67, t-test), and no difference in the overall change in performance between the first and the last block of 5 trials (p = 0.19, t-test). There was no difference in slopes between group in the regression model of performance vs. trials 6 to 50 (p = 0.63, t-test – see above for details of analysis).

Our simulations predict that visuo-spatial working memory integrity influences the degree of long-term forgetting after blocked schedules, but not after random schedules. Figure 8A illustrates the strong dependency of the figural Wechsler score upon long-term forgetting in the blocked schedule (Compare Figure 5A and 8A). A repeated ANOVA model with test as repeated factor and figural Wechsler as covariate showed significant long-term forgetting in the blocked schedule (p = 0.025) and a significant effect of the figural Wechsler on long-term forgetting (p = 0.0067). A similar analysis show no long-term forgetting in the random schedule (p = 0.55), and no effect of the figural Wechsler score on long-term forgetting (p = 0.56), again as predicted by our computer simulations (Compare 5B, and Figure 8B).

The influence of visuo-spatial working memory on long-term forgetting is well illustrated by classifying stroke individuals between high and low visuo-spatial working memory based on a cut-off of 7 on the figural Wechsler memory score. The difference between long-term forgetting in blocked and random schedule was significant in the high spatial working memory sub-groups (N = 5 high spatial working memory in blocked, N = 8 high spatial working memory in random, Mann-Whitney test, p = 0.042). However, there was no difference in long-term forgetting in the low spatial working memory sub-groups, (Mann-Whitney test, p = 0.40).

Finally, we verified that, in the individuals post stroke enrolled in the study, there was no correlation between the figural Wechsler memory score and any motor and sensory variables (maximum power force $p = 0.482$, UE Fugl-Meyer ROM $p = 0.480$, UE Fugl-Meyer Pain $p = 0.825$, UE Fugl-Meyer Sensory $p = 0.316$, UE Fugl-Meyer Motor $p= 0.839$, UE Fugl-Meyer Wrist $p = 0.330$, UEFugl-Meyer Hand $p =0.615$, FTHUE $p = 0.839$). There was no correlation of the figural memory score with the digital Wechsler memory score ($p > 0.87$). The only significant correlation between the figural score was with the MMSE ($r = 0.70$, $p <0.0005$). Furthermore, there was no correlation between long-term forgetting and any motor and sensory variables (maximum power force $p = 0.66$, UE Fugl-Meyer ROM $p = 0.34$, UE Fugl-Meyer Pain $p = 0.98$, UE Fugl-Meyer Sensory $p = 0.79$, UE Fugl-Meyer Motor $p= 0.2$, UE Fugl-Meyer Wrist $p = 0.31$, UEFugl-Meyer Hand $p =0.44$, FTHUE $p = 0.56$). Since the MMSE contains working memory components, this validates the use of the Wechsler figural memory score as a visuo-spatial working memory test in our study. These results indicate that it is the integrity of figural visuo-spatial working memory, not any motor or sensory impairment after stroke that lead to the observed changes in long-term forgetting following blocked training.

Discussion

Here, we replicated the CI effect in non-disabled participants and presented novel evidence that the CI effect can hold in participants with stroke affecting the motor system, but is modulated by the integrity of visuo-spatial working memory. Our results indicate that individuals with stroke with normal visuo-spatial working memory, like non-disabled individuals, exhibit less long-term forgetting of visuo-motor skills acquired in random training schedules than in blocked training schedules. In contrast, individuals with stroke with low visuo-spatial working memory exhibit little long-term forgetting after

either random or blocked schedules. Our results may explain why previous studies reported conflicting results on the CI effect in individuals with stroke (Cauraugh and Kim 2003; Hanlon 1996) as participants were not separated by low and high working memory capabilities.

The rather counter-intuitive effect of the integrity of visuo-spatial working memory on long-term retention following blocked schedules (the better the working memory the worse the long-term retention!) was predicted on a theoretical basis with our previous computational model of motor memory (Lee and Schweighofer 2009). Furthermore, we found no other motor or sensory variables that correlated with long-term forgetting after training in the blocked schedule or the integrity of visuo-spatial working memory. Thus, our combined computational and experimental results suggest that the integrity of visuo-spatial working memory is a crucial factor underlying the modulation of the CI effect in participants post-stroke in our experiment.

Although the CI effect has led to a considerable amount of research over almost a century (Magill and Hall 1990), its underlying mechanism has remained unclear. Three non-exclusive hypotheses have been proposed to explain the CI effect in motor learning. First, according to the "elaboration-distinctiveness" hypothesis, random training schedules allow inter-task comparison during the planning stage that lead to distinctive memory representations; e.g., (Cross et al. 2009; Immink and Wright 2001; Lin et al. 2008; Shea and Morgan 1979b). Second, according to the "deficient processing" hypothesis, blocked repetitions lead to reduced rehearsal or attention in later presentations, e.g. (Callan and Schweighofer 2010; Hintzman et al. 1973). Third, according to the "forgetting-reconstruction" hypothesis of the CI effect, forgetting between successive presentations of the same task during random training results in stronger memory representations (Lee and Magill 1983; Lee et al. 1985).

Here, we propose a novel mechanistic account of the CI effect in motor learning. Like in the "forgetting-reconstruction" hypothesis, our account of the CI effect relies on forgetting between

444 presentations of the same task during training. The specific mechanisms underlying the enhancement of
445 long-term memory differ in the forgetting-reconstruction hypothesis and in our model, however.
446 According to the forgetting-reconstruction hypothesis, forgetting in working memory between spaced
447 presentations necessitates retrieval from long-term memory, which increases long-term retention. In our
448 model, forgetting in visuo-spatial working memory between spaced presentations during training leads to
449 slower improvements in performance in random schedule than in blocked schedules. The resulting greater
450 errors during training benefit the update of the slow process, leading to better long-term retention. Note
451 that our account of the CI effect does not exclude additional explanations such as the "elaboration-
452 distinctiveness" and the "deficient processing" theories; further studies are needed to dissociate the
453 possible contributions of such mechanisms. Moreover, further studies are needed to determine the
454 putative neural substrates for the slow and fast processes. For example, we recently showed that the
455 neural substrates of memory consolidation depend on practice structure (Kantak et al. 2010).
456
457 Our results have implications for rehabilitation of patients with stroke. Although there is good
458 evidence that task training is effective for improving upper extremity function after stroke (Butefisch
459 1995; Kwakkel et al. 1999; Wolf et al. 2002; Wolf et al. 2006), none of these studies addresses the
460 "microscheduling" of individual tasks. Thus, although the use of random task schedule during training
461 has been advocated (Krakauer 2006), physical and occupational therapists rely on guidelines that simply
462 suggest inclusion of extensive and variable training without weighing heavily on individual capability;
463 e.g., (Bach-y-Rita and Balliet 1987; Lee et al. 1991). Here, our results suggest that patients with stroke
464 with normal visuo-spatial working memory should receive training schedules that mix tasks randomly.
465 Because such training is hard to implement in normal therapeutic situations, and places high demand on
466 the therapists, robots that can present functional tasks and can easily switch between these tasks during
467 training, could be developed - see our preliminary work in this direction (Choi et al. 2009). On the
468 contrary, and in a rather counter-intuitive manner, our results suggest that individuals with stroke with

poor visuo-spatial working memory can receive blocked training schedules with no compromise to long-term retention.

Our experiment has a number of limitations that need to be addressed in future work. First, our study included only a relatively small number of participants in each group, and needs replication with a larger sample size and different populations, such as the elderly. Here, we chose to study young healthy subjects as a control population and not (older) age matched controls because the elderly show decrease working memory capability, which may have led to a reduced CI effect in this population - see (Anguera et al. 2011). Two contextual interference studies have found a CI effect in motor tasks in older adults (Lin et al. 2007; Lin et al. 2010), Lin et al. 2010 directly compared young and elderly subjects on a serial reaction time task, and found the CI effect in both groups. Lin et al. 2007 found a CI effect in a subject population of similar ages as our participants post-stroke with motor tasks similar to ours in that subjects must produce different force patterns as a result of specific visuo-motor patterns. Second, although the young participants in our study were instructed to use their dominant hand, the participants post-stroke were instructed to use their most affected hand, which was or was not their affected hand before stroke. There is therefore the slight possibility that our results are due to not controlled handedness, although concordance was balanced across groups (see Table 2). Third, a prediction of the model is that poor visuo-spatial working memory will reduce the rate of performance improvement during acquisition in blocked practice. We found no correlation between the figural memory and the rate of learning in the stroke group however. This can be due to the large variability between and within participants at each trial during training in the stroke group compared to the non-disabled group (compare the shaded areas of Figures 6A and 7A). Increasing the sample size in motor tasks that lead to less trial-by-trial variability may be desirable. Fourth, because visuo-spatial working memory is thought to have a limited capacity, e.g., (Cowan 2001), it is possible that, in addition to, or in lieu of, shortened time-span, limited visuo-spatial working memory in our participants is due to a deficit in the number of items that can be stored in memory (our current model of motor memory cannot account for such limited storage mechanism). Fifth,

we were only able to obtain the MRI scans for a small subset of our participants. In future work, it would be most interesting to relate stroke characteristics, such as locations and volumes to the amount of CI effect that can be induced.

Similarly, our model, because of its simplicity, has a number of important limitations. First, like others, e.g. (Kording et al. 2007; Smith et al. 2006), we only attempted to model the common neuronal mechanism of error-driven motor adaptation or learning, but not the mechanism for specific types of motor adaptation or learning. As such, the model accounts for dual-adaptation data in eye movement, visuo-motor rotation, and force field adaptation – see (Lee and Schweighofer 2009). However, our model does not account for the effect of physiological factors, such as muscle mechanics, etc., of our specific experimental tasks. Second, while our computation model is a model of motor adaptation (where "adaptation" is the change in motor performance that allows the motor system to regain its former capabilities in altered circumstances), we used it here to account for visuo-motor learning of novel tasks. Such extension from adaptation to motor learning requires us to make two assumptions about motor learning in our experiment. The first assumption is that learning in our experiment is error-driven. Since we provided an error measure in the form of the actual force trajectory superimposed on the desired trajectory (Figure 1), this appears reasonable. In addition, there is also a large body of evidence that support the fact that skill learning is at least in part driven via errors (reviewed for instance in (Hikosaka et al. 2002). The second assumption is that skill learning, like motor adaptation, results from a combination of fast and slow memory processes – there is a large body of evidence that supports this view – see for review (Anguera et al. 2010; 2011; Anguera et al. 2009). The final, and perhaps most crucial limitation of our model in the current context, is that our model assumes that there is no interference/generalization between tasks in the slow processes. Thus, our model cannot reproduce any transfer of learning effect across tasks. This is clearly an over simplification in light of the similarities between the three tasks in our experiment (see Figure 2), and this prevented us to use the participant data to estimate the model parameters (which had to be hand-tuned instead). However, our simulation results

show that our model well accounts for the CI effect when performance across tasks are averaged. Further work will need to determine whether the CI effect occurs when several unique tasks, such as a force task, a digit manipulation task, and a bimanual task, etc., are given.

In sum, our combined theoretical and experimental results suggest a relationship between the integrity of visuo-spatial working memory and motor learning. Such a relationship between working memory and motor learning has been previously reported in a number of recent studies, e.g., (Anguera et al. 2010; Boyd and Winstein 2004; Keisler and Shadmehr 2010); our results add to and extend a body of work by showing that working memory is involved in the CI effect. Causal evidence for a role of visuo-spatial working memory in the CI effect in motor learning may be obtained via virtual lesion of the areas involved in visuo-spatial working memory via repetitive transcranial magnetic stimulation - see related (Tanaka et al. 2010).

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References

Anguera JA, Reuter-Lorenz PA, Willingham DT, and Seidler RD. Contributions of spatial working memory to visuomotor learning. *J Cogn Neurosci* 22: 1917-1930, 2010.

Anguera JA, Reuter-Lorenz PA, Willingham DT, and Seidler RD. Failure to engage spatial working memory contributes to age-related declines in visuomotor learning. *J Cogn Neurosci* 23: 11-25, 2011.

Anguera JA, Seidler RD, and Gehring WJ. Changes in performance monitoring during sensorimotor adaptation. *J Neurophysiol* 102: 1868-1879, 2009.

Bach-y-Rita P, and Balliet R editors. *Recovery from stroke. Stroke rehabilitation: the recovery of motor control*. Chicago,: Year Book Medical Publishers, Inc., 1987, p. 79-107.

Boyd LA, and Winstein CJ. Providing explicit information disrupts implicit motor learning after basal ganglia stroke. *Learn Mem* 11: 388-396, 2004.

Butefisch C, Hummelsheim, H, Denzler, P, Mauritz, KH. Repetitive training of isolated movements improves the outcome of motor rehabilitation of the centrally paretic hand. *J Neurol Sci* 130: 59-68., 1995.

Callan DE, and Schweighofer N. Neural correlates of the spacing effect in explicit verbal semantic encoding support the deficient-processing theory. *Hum Brain Mapp* 31: 645-659, 2010.

Cauraugh JH, and Kim SB. Stroke motor recovery: active neuromuscular stimulation and repetitive practice schedules. *J Neurol Neurosurg Psychiatry* 74: 1562-1566, 2003.

Choi Y, Gordon J, Kim D, and Schweighofer N. An Adaptive Automated Robotic Task-Practice System for Rehabilitation of Arm Functions After Stroke. *Robotics, IEEE Transactions on* 25: 556 - 568, 2009.

Cowan N. The magical number 4 in short-term memory: a reconsideration of mental storage capacity. *Behav Brain Sci* 24: 87-114; discussion 114-185, 2001.

Cross ES, Kraemer DJ, Hamilton AF, Kelley WM, and Grafton ST. Sensitivity of the action observation network to physical and observational learning. *Cereb Cortex* 19: 315-326, 2009.

Hanlon RE. Motor learning following unilateral stroke. *Arch Phys Med Rehabil* 77: 811-815, 1996.

Hawkins KA, Sullivan TE, and Choi EJ. Memory deficits in schizophrenia: inadequate assimilation or true amnesia? Findings from the Wechsler Memory Scale--revised. *J Psychiatry Neurosci* 22: 169-179, 1997.

Hikosaka O, Nakamura K, Sakai K, and Nakahara H. Central mechanisms of motor skill learning. *Curr Opin Neurobiol* 12: 217-222, 2002.

Hintzman DL, Block RA, and Summers JJ. Contextual associations and memory for serial position. *Journal of Experimental Psychology* 97: 220-229, 1973.

Immink MA, and Wright DL. Motor programming during practice conditions high and low in contextual interference. *J Exp Psychol Hum Percept Perform* 27: 423-437, 2001.

Joiner WM, and Smith MA. Long-term retention explained by a model of short-term learning in the adaptive control of reaching. *J Neurophysiol* 100: 2948-2955, 2008.

Kantak SS, Sullivan KJ, Fisher BE, Knowlton BJ, and Winstein CJ. Neural substrates of motor memory consolidation depend on practice structure. *Nat Neurosci* 13: 923-925, 2010.

Keisler A, and Shadmehr R. A shared resource between declarative memory and motor memory. *J Neurosci* 30: 14817-14823, 2010.

Kording KP, Tenenbaum JB, and Shadmehr R. The dynamics of memory as a consequence of optimal adaptation to a changing body. *Nat Neurosci* 10: 779-786, 2007.

Krakauer JW. Motor learning: its relevance to stroke recovery and neurorehabilitation. *Curr Opin Neurol* 19: 84-90, 2006.

Kwakkel G, Wagenaar RC, Twisk JW, Lankhorst GJ, and Koetsier JC. Intensity of leg and arm training after primary middle-cerebral-artery stroke: a randomised trial. *Lancet* 354: 191-196, 1999.

Lee JY, and Schweighofer N. Dual adaptation supports a parallel architecture of motor memory. *J Neurosci* 29: 10396-10404, 2009.

Lee TD, and Magill RA. The locus of contextual interference in motor-skill acquisition. *Journal of Experimental Psychology: Human Perception and Performance* 9: 730-746, 1983.

Lee TD, Magill RA, and Weeks DJ. Influence of practice schedule on testing schema theory predictions in adults. *Journal of Motor Behavior* 17: 283–299, 1985.

Lee TD, Swanson LR, and Hall AL. What is repeated in a repetition? Effects of practice conditions on motor skill acquisition. *Phys Ther* 71: 150-156, 1991.

Lin CH, Fisher BE, Winstein CJ, Wu AD, and Gordon J. Contextual interference effect: elaborative processing or forgetting-reconstruction? A post hoc analysis of transcranial magnetic stimulation-induced effects on motor learning. *J Mot Behav* 40: 578-586, 2008.

Lin CH, Sullivan KJ, Wu AD, Kantak S, and Winstein CJ. Effect of task practice order on motor skill learning in adults with Parkinson disease: a pilot study. *Phys Ther* 87: 1120-1131, 2007.

Lin CH, Wu AD, Udompholkul P, and Knowlton BJ. Contextual interference effects in sequence learning for young and older adults. *Psychol Aging* 25: 929-939, 2010.

Magill RA, and Hall KG. A review of the contextual interference effect in motor skill acquisition. *Human Movement Science* 9: 241-289, 1990.

Nixon SJ, Kujawski A, Parsons OA, and Yohman JR. Semantic (verbal) and figural memory impairment in alcoholics. *J Clin Exp Neuropsychol* 9: 311-322, 1987.

Pyle WH. Transfer and interference in card-distributing. *Journal of Educational Psychology* 10: 107-110, 1919.

Schmidt RA, and Lee TD. *Motor control and learning: a behavioral emphasis*. Champaign, Ill: Human Kinetics, 1999.

Shea JB, and Morgan R. Contextual interference effects on the acquisition, retention, and transfer of motor skills. *J exp psychol [Hum Learn]* 3: 179-187, 1979a.

Shea JB, and Morgan RL. Contextual interference effects on the acquisition, retention, and transfer of a motor skill. *Journal of Experimental Psychology* 5: 179-187, 1979b.

Smith MA, Ghazizadeh A, and Shadmehr R. Interacting adaptive processes with different timescales underlie short-term motor learning. *PLoS Biol* 4: e179, 2006.

Tanaka S, Honda M, Hanakawa T, and Cohen LG. Differential contribution of the supplementary motor area to stabilization of a procedural motor skill acquired through different practice schedules. *Cereb Cortex* 20: 2114-2121, 2010.

Tsuitsui S, Lee TD, and Hodges NJ. Contextual interferences in learning new patterns of bimanual coordination. *Journal of Motor Bahavior* 30: 1998.

Wechsler D. *Wechsler Memory Scale-revised*. New York: Psychological Corporation, 1987.

Winstein CJ, Merians AS, and Sullivan KJ. Motor learning after unilateral brain damage. *Neuropsychologia* 37: 975-987, 1999.

Winstein CJ, Merians, A, Sullivan, K. . Motor learning after unilateral brain damage. *Neuropsychologia* 37: 975-987, 1999.

Wolf SL, Blanton S, Baer H, Breshears J, and Butler AJ. Repetitive task practice: a critical review of constraint-induced movement therapy in stroke. *Neurologist* 8: 325-338, 2002.

Wolf SL, Winstein CJ, Miller JP, Taub E, Uswatte G, Morris D, Giuliani C, Light KE, and Nichols-Larsen D. Effect of constraint-induced movement therapy on upper extremity function 3 to 9 months after stroke: the EXCITE randomized clinical trial. *JAMA* 296: 2095-2104, 2006.

Figure Legends

Figure 1. Motor task. At each trial, one of three target force profiles was shown during the "ready" period. The specific force profile was selected according to a predetermined schedule (random or blocked). Two seconds later, a "GO" signal appeared and the participant was instructed to reach and grasp the apparatus and modulate the power grip force to approximate the target profile that lasted 2 seconds. The computer screen then became blank for 4 seconds, and feedback was shown for 4 seconds. Feedback included the actual force profile superimposed with the desired profile, the root mean squared error (RMSE) between the two profiles, as a well as a "best score", which reflected the smallest error so far, and was included for motivational purposes.

Figure 2. Examples of force trajectories for four participants for one task. From left to right: first trial of practice, first trial of immediate retention test, and first trial of delayed test. From top to bottom: representative participant post-stroke in blocked schedule, participant post-stroke in random schedule, non-disabled participant in blocked schedule, and non-disabled participant in random schedule. Gray line: desired force profile. Black line: actual force (in N) exerted by the participant during 2 seconds.

Figure 3. Computer simulations: CI effect in the "non-disabled model. Performance (black line), fast process (gray dot line), and slow process (light gray line) during blocked (A) and random schedule training (C). Immediate and long-term retention following blocked (B) and random schedule (D) training. Imm: Immediate test. Del: 24 hour delayed test. Notice the large forgetting following blocked training and slower performance improvement during random than during blocked training. The jitter in the fast process memory (reflected in performance) during random training in C was due to both decay and interferences between the tasks.

Figure 4. Computer simulations: reduced CI effect in a model with "poor visuo-spatial working memory". Performance (black line), fast process (gray dot line), and slow process (light gray line) during blocked (A) and random schedule training (C). Immediate and long-term retention following blocked (B) and random schedule (D) training. Imm: Immediate test. Del: 24 hour delayed test. In blocked schedules, there was little forgetting in the delayed retention test (B; compare with Figure 3B) because of relatively higher build-up of slow process and lower build-up of fast process during training (A; compare with Figure 3A). In random schedules, there was little difference during training (C) and testing (D) compared to the normal model (compare with Figure 3C,D).

Figure 5. Computer simulations: Forgetting measured at the delayed retention test as a function of the time constant of decay of fast process after either blocked (A) or random (B) schedule for two tasks. Overall, and notably for larger time constants, there was less forgetting following random schedule than blocked schedule. However, for smaller time constants, forgetting was comparable following random and blocked schedule.

Figure 6. Data: CI effect in non-disabled participants. Performance (mean and SE) during blocked (A) and random (C) training. Immediate and long-term retention following blocked (B) and random (D) training.

Figure 7. Data: CI effect in participants post-stroke. Performance (mean and SE) during blocked (A) and random (C) training. Immediate and long-term retention following blocked (B) and random (D) training.

Figure 8. Data: Forgetting in individuals post-stroke in a 24 hour post-training period as a function of Wechsler visual memory score (figural) following training in either blocked (A) or random schedule (B)

in the individuals post-stroke who participated in the study. Black lines: regression line. Gray line in B: robust regression line (with default weighting function in Matlab *robustfit* function) - the robust regression line is superimposed to the regression line in A. Compare to the computer simulations of Figure 5.

Tables

Table 1: Characteristics of the non-disabled individuals. * $p < 0.05$.

Characteristics	Blocked (n=12)	Random (n=11)	p-value
Men	6	6	$p > 0.1$
Age (yrs.)	25.5 ± 1.86	26.7± 2.65	$p > 0.1$
Power force (N)	863 ± 99	794 ± 111	$p > 0.1$
Wechsler Figural(10)	8.58 ± 0.29	8.33 ±0.33	$p > 0.1$

692

693 **Table 2:** Characteristics of the individuals post-stroke.

Characteristics	Blocked (n=12)	Random (n=13)	p-value
Men	8	9	p>0.1
Age (years)	61.25±13.92	54.58±13.39	p>0.1
Left Hemiparesis	6	4	p>0.1
Concordance	7	5	p>0.1
Months post onset	39.25±16.45	25.83±22.32	p>0.1
Power force (N)	462 ± 67	326 ± 29	**p = 0.082**
UEFugl-Meyer			
ROM (max = 24)	22.58±1.83	22.25±1.76	p>0.1
Pain (max =24)	24.00±0.00	23.25±2.30	p>0.1
Sensory (max =12)	12.00±0.00	11.00±2.23	p>0.1
Motor (max = 66)	55.00±8.98	54.00±7.01	p>0.1
Wrist (max = 10)	9.10±2.81	8.00±3.28	p>0.1
Hand (max = 14)	12.25±1.54	11.58±2.31	p>0.1
FTHUE	14.50± 3.53	14.91± 2.94	p>0.1
MMSE (max = 30)	29.25±1.21	29.41±0.90	p>0.1
Wechsler			
Digital (max = 24)	16.83±4.71	16.08±3.17	p>0.1
Figural (max = 10)	6.16±1.69	6.67±1.97	p>0.1

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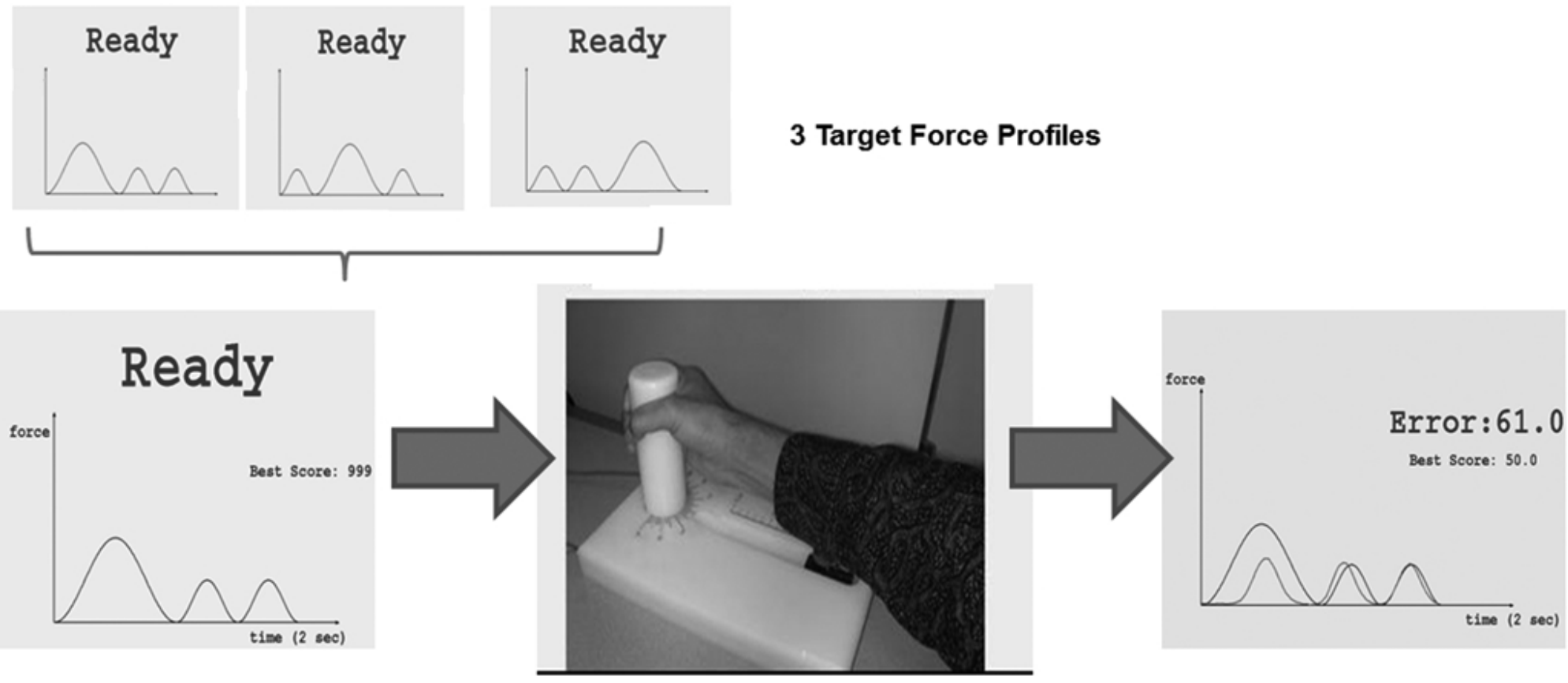
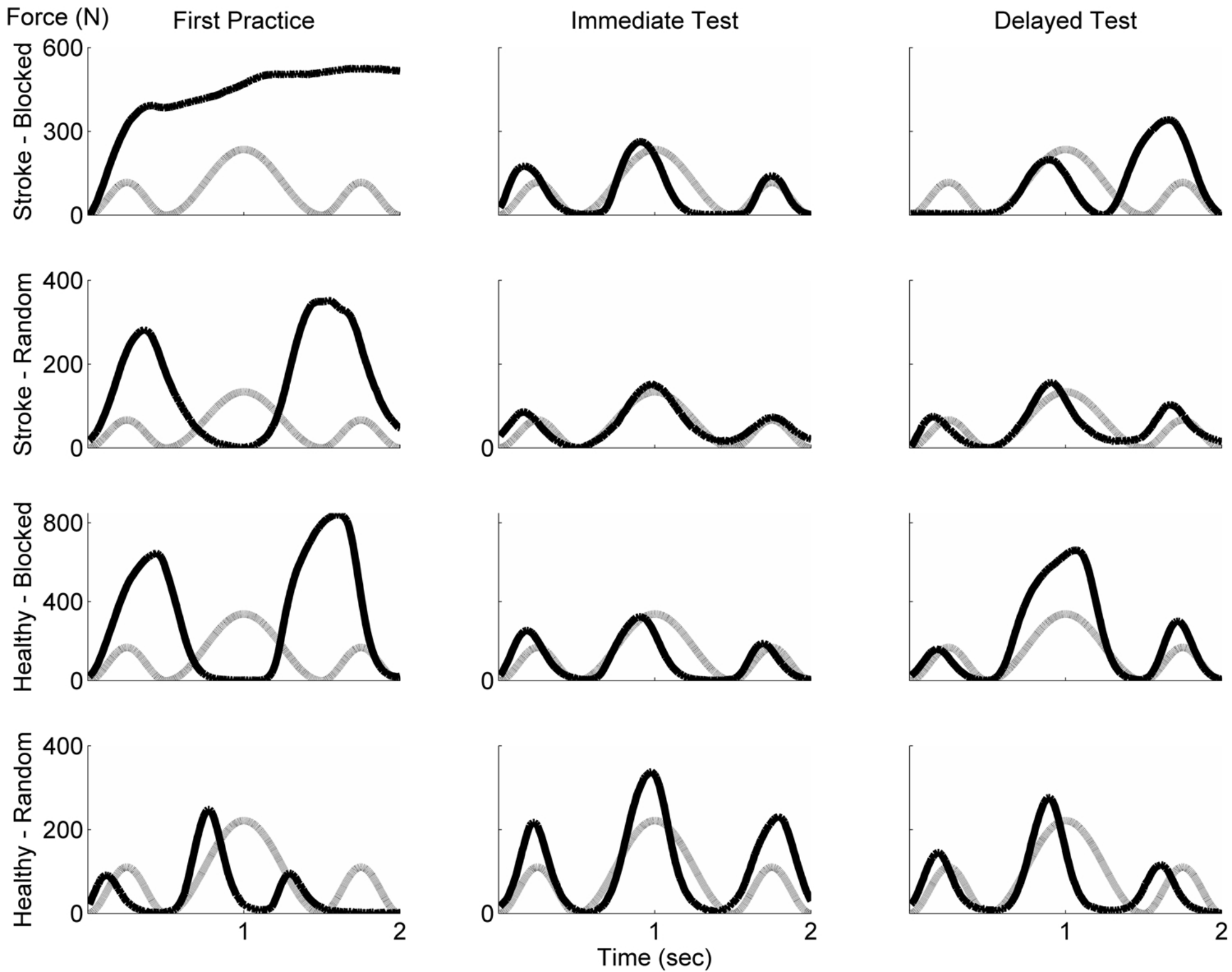
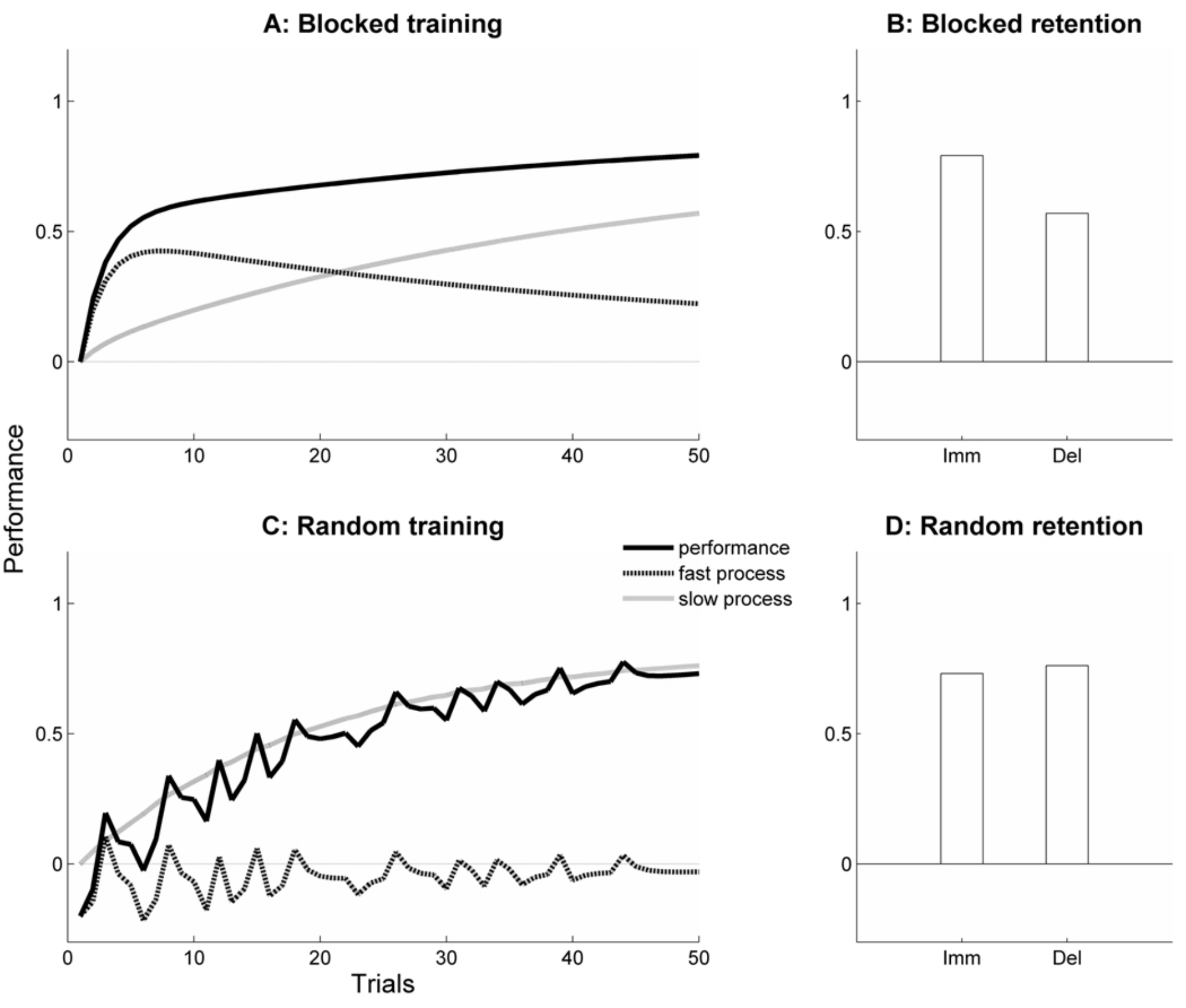
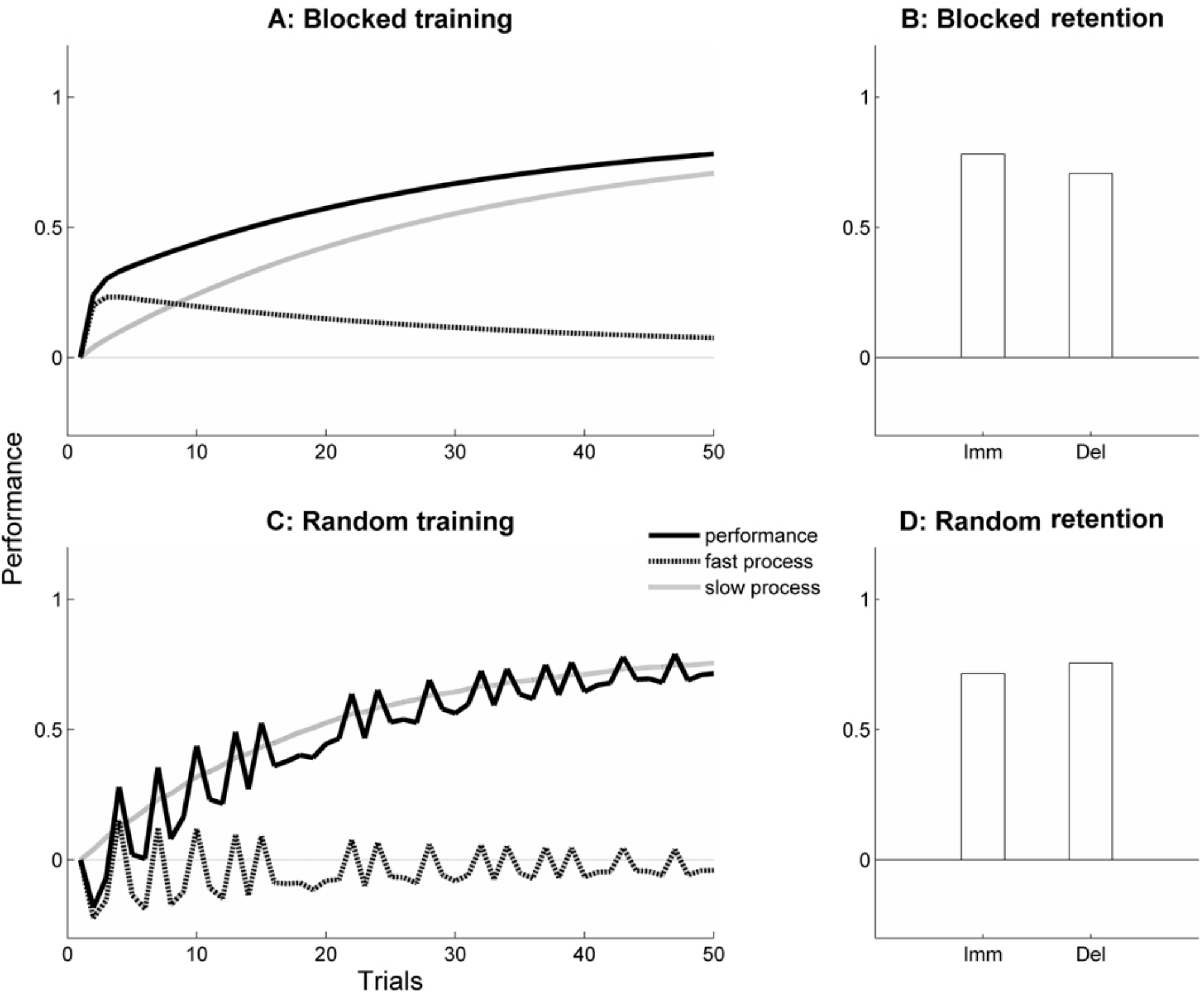
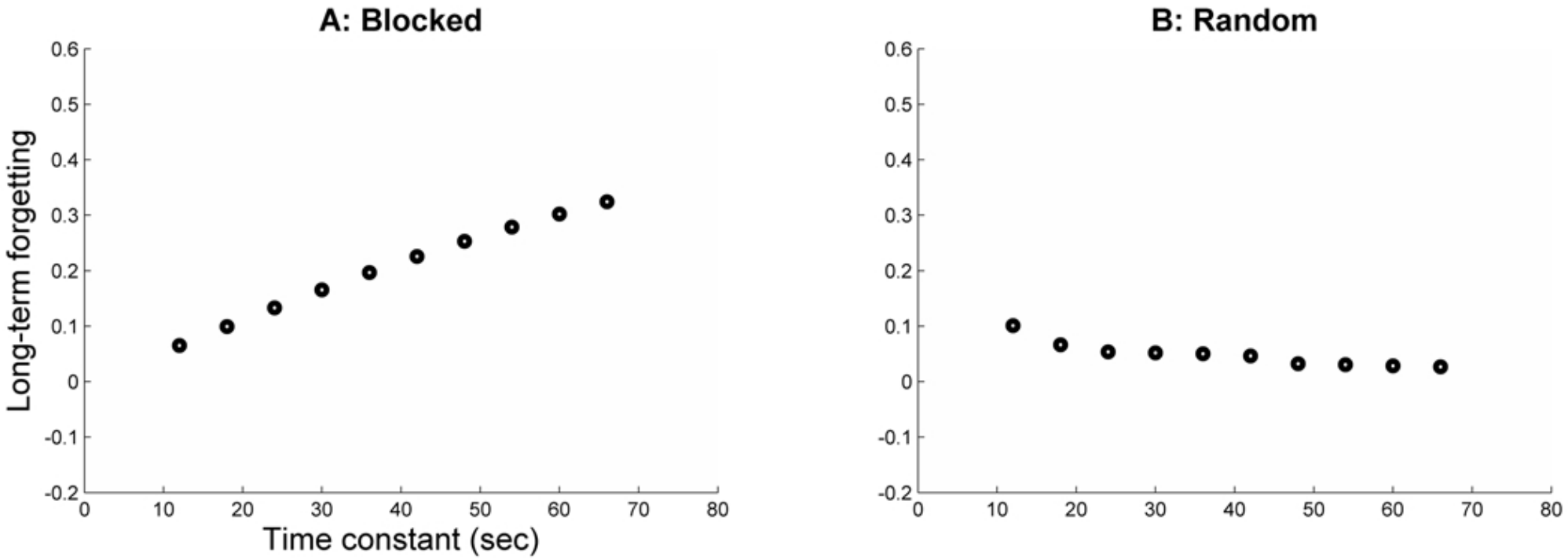
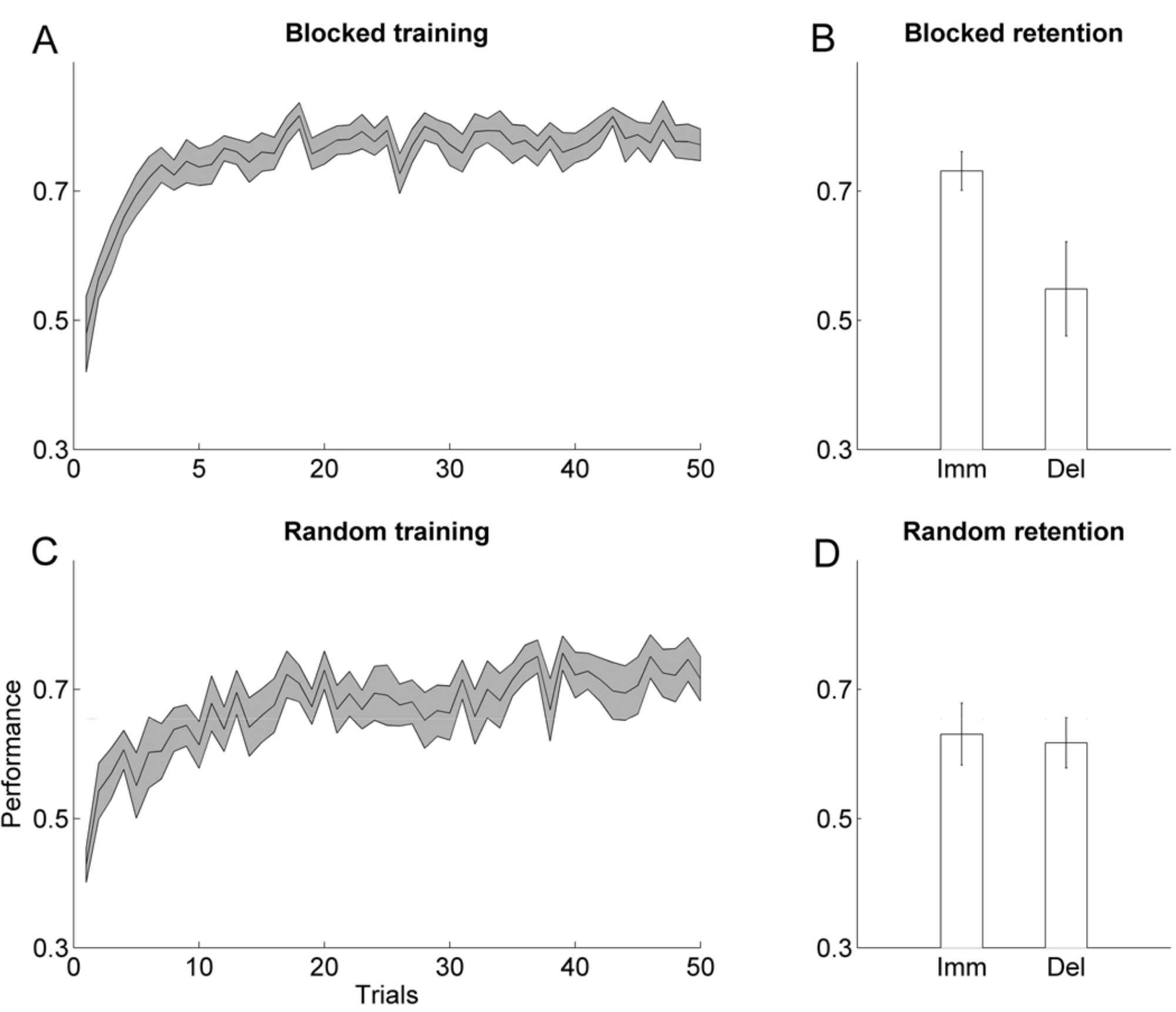

Ready
Ready
Ready
3 Target Force Profiles
Ready
force
Best Score: 999
time (2 sec)
force
Error:61.0
Best Score: 50.0
time (2 sec)

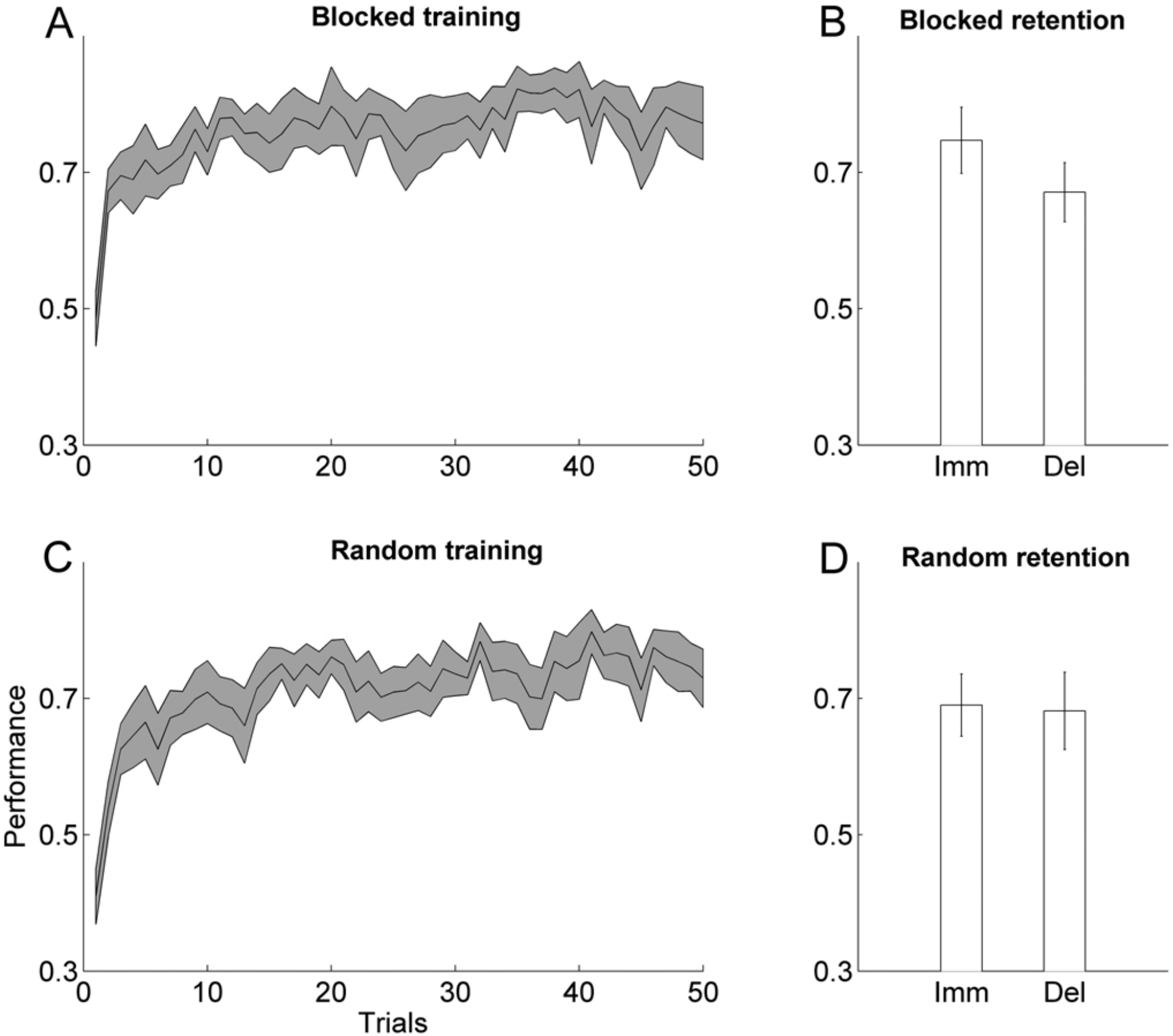

Force (N)
First Practice
Immediate Test
Delayed Test
Stroke - Blocked
Stroke - Random
Healthy - Blocked
Healthy - Random
600
300
0
400
200
0
800
400
0
400
200
0
1
2
Time (sec)

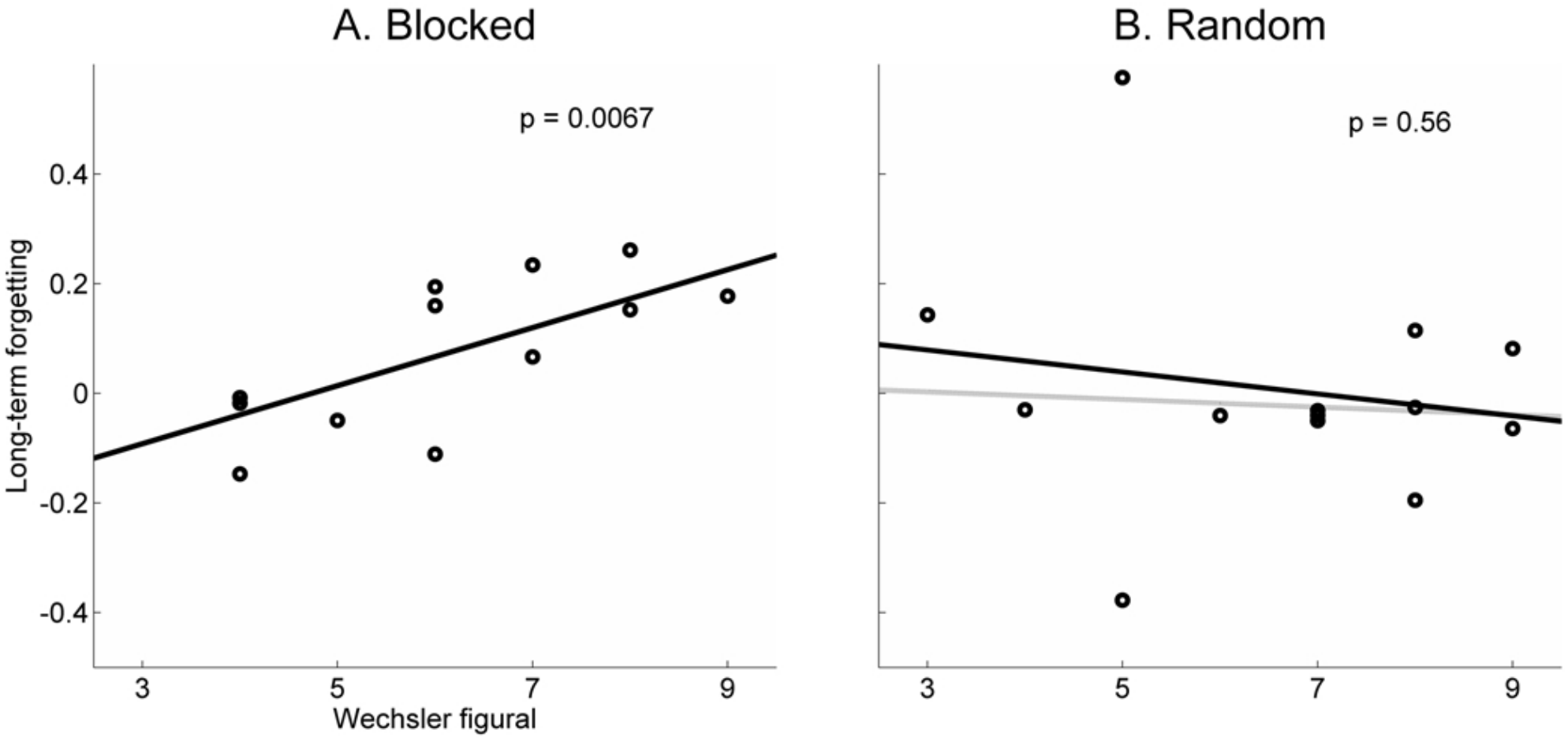

A: Blocked training
B: Blocked retention
C: Random training
D: Random retention
Performance
Trials
performance
fast process
slow process
Imm
Del
0
0.5
1
10
20
30
40
50


A: Blocked training
B: Blocked retention
C: Random training
D: Random retention
Performance
Trials
performance
fast process
slow process
1
0.5
0
0
10
20
30
40
50
Imm
Del


A: Blocked
B: Random
Long-term forgetting
Time constant (sec)
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
0
10
20
30
40
50
60
70
80


A
Blocked training
B
Blocked retention
C
Random training
D
Random retention
Performance
Trials
0.3
0.5
0.7
0
5
10
20
30
40
50
Imm
Del


A
Blocked training
B
Blocked retention
C
Random training
D
Random retention
Performance
Trials
0.3
0.5
0.7
0
10
20
30
40
50
Imm
Del


A. Blocked
B. Random
p = 0.0067
p = 0.56
Long-term forgetting
0.4
0.2
0
-0.2
-0.4
3
5
7
9
Wechsler figural